

POLYSACCHARIDE FOR ENHANCEMENT OF CARDIAC OUTPUT

BACKGROUND OF THE INVENTION

The present invention relates generally to therapeutic methods and materials useful in selectively providing desirable hemodynamic effects in animals, including humans. More specifically the invention relates to administration of fluids containing relatively small amounts of certain selected polysaccharide materials to the blood of a patient for the purpose of enhancing cardiac output without substantially increasing blood volume or generating inotropic, chronotropic or vaso-active effects.

The prior art is profuse with proposals of methods and materials for developing curative, ameliorative and prophylactic effects respecting circulatory system disorders of widely differing etiology. Clearly of interest with respect to the background of the present invention are the art's many proposals for restoring and/or enhancing cardiac output to healthy and failing hearts upon the occurrence of underperfusion of vital tissue as in traumatic and functional hypovolemia, syncope and cardiogenic shock. A separate body of information has been developed relating to ameliorative and/or prophylactic treatment of atherosclerotic disorders. Of particular interest to the background of the invention are prior proposals for treating and preventing atherosclerosis by administration of substances suspected of having beneficial rheological effects on circulatory fluids.

I. Treatment Of Tissue Underperfusion

Included among the proposals of the art for treating underperfusion of vital tissues are such standard procedures as administering sympathomimetic vasopressive agents to effect elevation of coronary perfusion pressure; administering inotropic agents to enhance myocardial contractility; administration of chronotropic agents to alter cardiac periodicity; and application of intra-aortic counterpulsation techniques. The advantages and disadvantages of such procedures have been explored in detail. See, e.g., Weiner, "Rational Therapeutic Approach to Cardiogenic Shock" in *Cardiovascular Drug Therapy*, K.L. Melmon, editor, F.A. Davis, Philadelphia, 1974, pp. 223-237.

Where there has been external loss of blood, plasma or extracellular fluid or internal sequestration of plasma in areas of inflammation, the standard treatment procedure has been rapid additive restoration of blood volume to "normal" levels. Plasma replacement fluids capable of effecting such restoration are well known and include water solutions of dextran, albumin, dextrose and other solutes with osmotic and oncotic pressures similar to that of plasma. Selection of solutions for use as plasma replacement fluids is made with great care. The choice of any particular solute is often complicated by the potential for increased capillary permeability to solutes (e.g., albumin) during hemorrhagic shock, the potential for exceeding tissue oncotic pressure and likelihood of interstitial pulmonary edema attendant administration of any noncolloidal fluids. While research on solutes has proceeded for many decades, very few solutions have received widespread clinical use.

Among the many proposals for plasma substitutes made in the last 25 years is that of Benjamin, et. al, *Rev. Can. Biol.*, 10, 215-221 (1951) which discloses a saline solution including an alcohol-extracted okra plant muci-

lage. This "2% okra plasma" was reportedly administered to hemorrhaged dogs, in amounts equal to blood lost. The animals, while profoundly anemic and deficient in plasma proteins, were said to have experienced substantial restoration of blood pressure and circulatory volume—sufficient to maintain vital functions until restoration of lost blood components could be effected.

II. Drag Reducing Agents

Knowledge of the capacity of certain polymers to reduce turbulent flow of solvents in tubes has prompted various proposals that natural and synthetic polymeric agents be administered to animal circulatory systems to diminish turbulence suspected to exist in arterial flow.

Proposals for administering polymeric "drag reducing" agents to blood have consistently emphasized that the additives would have clinical potential only in diminishing resistance to blood flow in those regions of the circulatory system where turbulence is likely to occur. Alternatively stated, the drag reducing potential of polymers is believed exclusively applicable to provide a benefit in large blood vessels and regions of arterial irregularity where velocity and vessel diameters would admit to turbulence. The additives are not expected to decrease resistance to flow in normal arteries wherein flow is laminar in character. [See, e.g., Stein et al., *Medical Research Engineering*, 11: 6-10 (1972); cf., Driels, et al, *Nature*, Vol. 259, No. 5542, pp. 389-90 (1976)]. Despite consistent authority to the effect that arterial blood flow is probably "disturbed" but not truly turbulent [see, e.g., Yellin, "Laminar-Turbulent Transition Process In Pulsatile Flow", *Circulation Research*, Vol. XIX, 791-804, 803 (1966)] suggestions for use of turbulence reducers in one form or another continue to be made.

U.S. Pat. No. 3,590,124 by Hoyt proposes the addition of 5-100 parts per million of high molecular weight water-soluble polyethylene oxides, polyacrylamides and linear polysaccharides to such blood transfusion fluids as dextran solutions, normal saline and liquid human plasma. The projected result of such practice is rather vaguely stated to be a reduction of turbulent friction within the transfusion fluid additive itself and a resultant reduction of body pumping requirements for the person receiving the transfusion. Polymers assertedly useful in such a manner are those exhibiting more or less classical drag reducing properties such as were catalogued by Hoyt in *Polymer Letters*, Vol. 9, pp. 851-862 (1971). Expectedly, the claimed advantages of the aforesaid patent were attributed to the use of those materials (such as selected high molecular weight polyethylene oxides) which commonly exert the most powerful influences on turbulent flow hydrodynamics in pipes, i.e., provide maximum drag reduction of water solutions at very small concentrations of 100 ppm or less.

Recent investigations into potential biomedical applications of polymeric drag reducing agents (see, e.g., Paper H2, Int'l Conf. on Drag Reduction, 1974, Cambridge, England, pages 17-27) provide reports of in vitro turbulence reduction by 40 ppm polyacrylamide additions to pooled blood samples. Other preliminary reports have dealt with the effect of drag reducing agents in decreasing turbulence in oscillatory flow; in diminishing destruction of red blood cells during extracorporeal circulation; and in lessening plaque accumulation in rabbit arterial tissue.